

In the Claims

NE Please cancel claims 1-17 and 22-49⁸, without prejudice or disclaimer.

Please amend the following claim:

18. (Amended) A method of screening for a modulator [modulators] of calpain function comprising [the steps of]:

- A1
- a) obtaining a [an] calpain polypeptide;
 - b) determining a standard activity profile of the calpain polypeptide;
 - c) contacting the calpain polypeptide with a putative modulator; and
 - d) assaying for a change in the standard activity profile.

Please add the following claims:

49
50. The method of claim 19, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

50
51. The method of claim 50, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.

52. A method of screening for a modulator of calpain function comprising:

- 52
- a) obtaining an calpain polypeptide;
 - b) contacting the calpain polypeptide with a putative modulator; and
 - c) assaying for modulation of calpain function by the putative modulator.

52
53. The method of claim 52, wherein the calpain polypeptide is a calpain 10 polypeptide.

53
54. The method of claim 53, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

54
55. The method of claim 52, further comprising determining a standard activity profile of the calpain polypeptide.

55-56. The method of claim 55, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

56-57. The method of claim 56, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.

57-58. The method of claim 56, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile.

58-59. The method of claim 52, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.

59-60. The method of claim 59, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60-61. The method of claim 52, wherein obtaining the calpain polypeptide comprises obtaining a cell containing the polypeptide.

61-62. The method of claim 61, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.

62-63. The method of claim 62, wherein the cell is a pancreatic cell.

63-64. The method of claim 63, wherein the pancreatic cell is comprised in an isolated pancreatic islet.

64-65. The method of claim 63, wherein the cell is a β -cell.

65-66. A method of screening for a modulator of calpain function comprising:
a) obtaining an calpain-encoding nucleic acid segment;

- b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
- c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
- d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and
- e) assaying for a change in the transcription and translation activity.

66-67. The method of claim 66, wherein the calpain-encoding nucleic acid segment encodes calpain 10.

67-68. A calpain modulator prepared by a process comprising screening for a modulator of calpain function comprising:

- a) obtaining an calpain polypeptide;
- b) determining a standard activity profile of the calpain polypeptide;
- c) contacting the calpain polypeptide with a putative modulator; and
- d) assaying for a change in the standard activity profile.

68-69. The modulator of claim 68, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.

69-70. The modulator of claim 68, wherein the calpain polypeptide is a calpain 10 polypeptide.

70-71. The modulator of claim 69, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

71-72. The modulator of claim 68, wherein the modulator of calpain function is a modulator of a calpain polypeptide.

72-73. The modulator of claim 72, wherein the calpain polypeptide is a calpain 10 polypeptide.

73 74. The modulator of claim 73, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

74 75. The modulator of claim 68, wherein the modulator of calpain function is an agonist or antagonist of a calpain polypeptide.

75 76. The modulator of claim 75, wherein the modulator of calpain function is an inhibitor of a calpain polypeptide.

76 77. The modulator of claim 76, wherein the modulator inhibits calpain I and/or calpain II.

77 78. The modulator of claim 76, wherein the modulator is calpeptin.

78 79. The modulator of claim 76, wherein the modulator is calpain inhibitor 2 (ALLM).

79 80. The modulator of claim 76, wherein the modulator of calpain function is a protease inhibitor.

80 81. The modulator of claim 80, wherein the protease inhibitor is a thiol protease inhibitor.

81 82. The modulator of claim 81, wherein the thiol protease inhibitor is E-64-d.

82 83. The modulator of claim 68, further defined as a method comprising inhibiting calpain activity in a β -cell with a modulator of calpain function.

83 84. The modulator of claim 68, further defined as a method comprising stimulating calpain activity in a muscle cell or fat cell with a modulator of calpain function.

84 85. The modulator of claim 68, further defined as a method comprising stimulating calpain activity in a fat cell or muscle cell with a modulator of calpain function and inhibiting calpain activity in a β -cell with a modulator of calpain function.

85 86. A calpain modulator prepared by a process comprising screening for a modulator of calpain function comprising:

- a) obtaining a calpain-encoding nucleic acid segment;
- b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
- c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
- d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and
- e) assaying for a change in the transcription and translation activity.

86 87. The method of claim 86, wherein the calpain-encoding nucleic acid segment encodes calpain 10.

87 88. A method of treating diabetes by modulating the function of one or more calpains in at least one of a β -cell, muscle cell, or fat cell with a modulator of calpain function, wherein the modulator is prepared by a process comprising screening for a modulator of calpain function comprising:

- a) obtaining a calpain-encoding nucleic acid segment;
- b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
- c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
- d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and
- e) assaying for a change in the transcription and translation activity.

88 89. The method of claim 88, wherein the calpain-encoding nucleic acid segment encodes calpain 10.

89⁹⁰. A method of treating diabetes by modulating the function of one or more calpains in at least one of a β -cell, muscle cell, or fat cell with a modulator of calpain function, wherein the modulator is prepared by a process comprising screening for modulators of calpain function comprising:

- a) obtaining an calpain polypeptide;
- b) determining a standard activity profile of the calpain polypeptide;
- c) contacting the calpain polypeptide with a putative modulator; and
- d) assaying for a change in the standard activity profile.

90⁹¹. The method of claim 90, wherein the modulator of calpain function is a modulator of a calpain polypeptide.

91⁹². The method of claim 91, wherein the calpain polypeptide is a calpain 10 polypeptide.

92⁹³. The method of claim 92, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

93⁹⁴. The method of claim 91, wherein the modulator of calpain function is an agonist or antagonist of a calpain polypeptide.

94⁹⁵. The method of claim 91, wherein the modulator of calpain function is an inhibitor of a calpain polypeptide.

95⁹⁶. The method of claim 95, wherein the modulator inhibits calpain I and/or calpain II.

96⁹⁷. The method of claim 95, wherein the modulator is calpeptin.

97⁹⁸. The method of claim 95, wherein the modulator is calpain inhibitor 2 (ALLM).

98⁹⁹. The method of claim 95, wherein the modulator of calpain function is a protease inhibitor.

99¹⁰⁰. The method of claim 99, wherein the protease inhibitor is a thiol protease inhibitor.

100¹⁰¹. The method of claim 100, wherein the thiol protease inhibitor is E-64-d.

101¹⁰². The method of claim 90, further defined as a method comprising inhibiting calpain activity in a β -cell with a modulator of calpain function.

102¹⁰³. The method of claim 90, further defined as a method comprising stimulating calpain activity in a muscle cell or fat cell with a modulator of calpain function.

103¹⁰⁴. The method of claim 90, further defined as a method comprising stimulating calpain activity in a fat cell or muscle cell with a modulator of calpain function and inhibiting calpain activity in a β -cell with a modulator of calpain function.

104¹⁰⁵. The method of claim 90, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

105¹⁰⁶. The method of claim 105, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.

106¹⁰⁷. The method of claim 105, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile.

107¹⁰⁸. The method of claim 90, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.

108¹⁰⁹. The method of claim 108, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.